REMARKS

In the Office Action dated December 11, 2006, the Examiner: (1) rejects claims 6 and 27 – 29 under 35 U.S.C. § 112, ¶ 1 for an alleged lack of written description; (2) rejects claims 43 – 60 under 35 U.S.C. § 112, ¶2 for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention; (3) rejects claims 1 and 38 – 60 under 35 U.S.C. § 112, ¶2 for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention; (4) rejects claims 6 and 27 – 29 under 35 U.S.C. § 101; and (5) rejects claims 6 and 27 –29 under 35 U.S.C. § 102(e) as being anticipated by McSwiggen *et al.* Applicants have amended the claim set above and submit that in view of those amendments and the arguments presented below, the claims are patentable.

Summary of Amendments

Applicants' invention as embodied in the claims as amended is directed to methods for selecting siRNA and the development of algorithms that assist in these methods. Through the use of these methods, a person of ordinary skill can increase the likelihood that an siRNA that is selected will be functional.

Applicants have amended claim 1 to provide that the candidate siRNA that is selected in subsection (d) is selected from the set of candidate siRNA molecules of step (b). Support for this amendment may be found in the previously pending claim itself, as well as on pages 41 – 44 of the specification and in figures 6a and 6b. Claim 1 has been further amended to replace the term "nucleoside" with "nucleotide," and the term "substantially" with "79%." The claim has also been amended in step (c), subsection (iv) to add the term "present." Support for these amendments may be found in previously pending claim 1 and on page 17, line 7 –16.

Applicants have amended claim 6 in two primary ways. First, Applicants have amended claim 6 to provide that the method provides an output to a user or computer storage device that comprises either a value generated by the algorithm or provides the relative ranking of a plurality of candidate siRNAs to which the algorithm has been

applied. Support for this amendment may for example, be found within Example V on page 69, line 7 – page 70 line 10, reflecting the generation of a list of the top 10 siRNA for Bcl-2 that were generated by Formula VIII, and within Example VI and Table V, page 70, line 13 – page 73, line 4, providing values generated by Formulas VIII and IX as applied to a number of targets.

Applicants have also amended claim 6 to provide that the at least one variable comprises the presence or absence of a particular base at a particular position of positions 1 – 19, that for siRNA of 20 – 30 bases, positions 1 – 19 refer to the nineteen 3' most bases within a sequence and that any additional bases occupy positions $^{-}1$ to $^{-}11$ of the sense region. Support for this amendment may be found on page 23, lines 6 – 14 (defining positions 1 – 19 and $^{-}1 – ^{-}11$). Formulas I – IX demonstrate examples of algorithms containing variables that reflect the presence or absence of particular bases at particular positions 1 – 19.

Applicants have amended claims 27 – 29 to provide for proper dependency on claim 6, and have added the limitation "contiguously in a stretch of four or more units" to describe that the variable of the number of times that a nucleotide repeats is relevant for the algorithm if it repeats at least four times in a row. Support for this amendment may be found on page 32, lines 14 -19.

Applicants have amended claim 43 in two primary ways. First, Applicants have amended subsection (c) to clarify how positions 1 – 19 are defined when the sequence contains 20 – 30 bases. Support for this amendment may be found on page 23, lines 6 – 14 (defining positions 1 – 19 and $^{-}1 – ^{-}11$). Second, Applicants have amended step (d) to clarify that the candidate is selected from the set described in step (b). Support for this amendment may be found in the previously pending claim itself, as well as on pages 41 – 44 of the specification and figures 6a and 6b.

Applicants have amended claims 44 – 60 to replace uses of the term "region" with the term "sequence" in order to provide for proper antecedent basis.

Applicants have also included other minor amendments to render the claims internally consistent and to provide proper antecedent basis.

No new matter has been added to any of the claims.

Response to rejection based on written description

The Examiner rejects claims 6 and 27 – 29 for failing to satisfy the written description requirement because of the inclusion of the limitations "the presence or absence of one or more particular nucleotides at one or more particular positions, and the number of time that the same nucleotide repeats within a given sequence." (Page 3 of Office Action) Applicants have amended the rejected claims and for the reasons provided below submit that in view of the amendments, the claims are patentable.

First, with respect to the limitation of "the presence or absence of one or more particular nucleotides at one or more particular positions," Applicants have amended claim 6 to recite that the presence or absence of the nucleotide is at positions 1 – 19 within a duplex of 19 – 30 bases. Applicants have also recited within the claim how to define a position when the duplex contains 20 – 30 base pairs.

In the specification, Applicants have described how they determined whether the presence or absence of a particular nucleotide would have a positive or negative correlation with gene silencing. *See e.g.*, page 38, line 18 – page 40, line 25, including Table IV. The specification also recites:

> The methods for obtaining the seven criteria embodied in
> Table IV are illustrative of the results of the process used to
> develop the information for Formulas VIII and IX. Thus
> similar techniques were used to establish the other variables
> and their multipliers. As described above, basic statistical
> methods were use to determine the relative values for these
> multipliers.

Page 41, lines 4 – 9 of the specification. This method is described in detail on pages 40, line 1 – page 41, line 22. Thus, the specification provides support for the amendment.

Moreover, Applicants note that there are only seventy-six possible independent variables (4 * 19) for these positions, and that they have disclosed in formulas VII and IX (page 28 of the specification) thirty-seven specific variables that refer to the presence or absence of a particular base at a particular position.[1]

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[1] Each of the nineteen positions can have one of four bases, and Applicants are claiming (in claim 6) the development of algorithms that use these types of variables. Thus, there are 76 possible variables. By contrast there are 4^{19} combinations of variables.

Second with respect to the limitation of how many times a nucleotide repeats, Applicants have deleted reference to this limitation in claim 6 and amended claims 27 – 29 by specifying that this limitation refers to "the number of times that the same nucleotide repeats contiguously in a stretch of four or more units within a given sequence." As noted above, support for this amendment may be found on page 32, lines 14 – 19.

In view of the amendments to claims 6 and 27 – 29, Applicants respectfully submit that this rejection should be withdrawn.

Response to first rejection based on alleged failure to particularly point out and distinctly claim the subject matter that Applicants regard as the invention

The Examiner rejects claims 43 – 60 for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention because it is unclear what happens when the sequence is greater than 19 bases. Without expressing an opinion as to the merits of the rejections, Applicants have amended claim 43 to specify that the siRNA may be from 19 – 30 bases and that when there are more than 19 bases, the 20th to 30th bases occupy positions $^{-}1$ to $^{-}11$, which are located 5' of position 1 of the sense sequence. Thus, extending the siRNA by an additional base that is located 5' of the sense sequence of a 19-mer to make a 20-mer would not change the numbering of a position. Support for this amendment may be found in the specification on page 22, lines 30 – 35.

In view of the amendment to claim 43, Applicants submit that the Examiner's rejection is no longer applicable and should be withdrawn.

Response to second rejection based on alleged failure to particularly point out and distinctly claim the subject matter that Applicants regard as the invention

The Examiner rejected claims 1 and 43 and being vague and indefinite because they are unclear as to whether the candidate siRNA in step (d) is selected from the set generated in step (b). Applicants have amended step (d) of claims 1 and 43 to recite that the candidate siRNA that is selected is chosen from the set recited in step (b).

Response to Rejection under 35 U.S.C. § 101

The Examiner rejected claims 6 and 27 – 29 under 35 U.S.C. § 101 for failing to produce a concrete tangible result. The Examiner has noted that the rejection could be overcome by reciting that a result of the method is outputted to a display or memory or another computer on a network or to a user, or by including a physical transformation.

In accordance with the Examiner's suggestions, Applicants have amended step (d) of claim 6 to provide that the algorithm is outputted to a user or a computer. Support for this amendment may for example, be found on page 27, line 23 – page 28, line 2; page 32, lines 14 –16 and 27 –28. In view of the amendment, Applicants respectfully request that the rejection be withdrawn.

Response to Rejection under 35 U.S.C. § 102(e)

The Examiner rejects claims 6 and 27 – 29 over McSwiggen. As noted above Applicants have amended claim 6 to include the limitation that at least one variable must reflect the presence or absence of one particular nucleotide at at least one particular position of positions 1 – 19 within the sense sequence and deleted all other variables.

The passage of McSwiggen that the Examiner cites does not teach, disclose or otherwise suggest focusing on the presence or absence of particular nucleotide at a particular position within positions 1 – 19. At most, McSwiggen discloses using dinucleotide sequences AA, TT and UU, which are meant to be tails, and not sequences within the duplex region. Moreover, even if McSwiggen were interpreted as suggesting that AA, TT or UU should be present at positions 18 – 19, this disclosure does not teach, disclose or otherwise suggest any value in focusing separately on any individual position within a sense sequence as is recited by Applicants' claim 6 or considering that the presence of A as opposed to U may have a different effect on functionality when present at a particular position. Thus, neither it nor any other part of McSwiggen teaches, discloses or otherwise suggests Applicants' invention as embodied in claim 6.

Conclusion

All of the Examiner's rejections have been fully traversed and addressed. Accordingly, Applicants respectfully request allowance of the pending claims.

Applicants submit that no fee is required in connection with the filing of this Amendment and Reply. If any fee is deemed necessary, please charge Deposit Account No. 11-0171.

Respectfully submitted,

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